Opioid Agonist Treatment During Pregnancy: Is it Time to Revisit Tapering or Detoxification?

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• The American Society of Addiction Medicine (ASAM) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
Designation Statement

• The American Society of Addiction Medicine (ASAM) designates this enduring material for a maximum of one (1) AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

  ▪ Date of Release: March 31, 2016
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System Requirements

• In order to complete this online module you will need Adobe Reader. To install for free click the link below:
Target Audience

- The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.
Educational Objectives

At the conclusion of this activity participants should be able to:

• Discuss the history and rationale behind current recommendations for the management of opioid use disorder during pregnancy
• Critically assess individual patient risk factors and whether that affects management and treatment of opioid use disorder in pregnancy
• Describe the relationships between poor maternal and fetal outcomes with retention in treatment, relapse, and prenatal care
Disclosure

Methadone and buprenorphine are both FDA category C medications. Use in pregnancy is neither specifically approved nor considered off-label.

The contents of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose this information.
Mrs. S. is a 32 year old female, G1P0, 11 weeks gestation, presenting for initial OB visit.

- Hx of low back pain from facet syndrome only partially relieved s/p facet rhizotomy 2 years ago
- Hx of allergy to NSAIDS
- Prescribed oxycodone 5 mg q 6h prn by PCP 2 years ago, takes orally as directed
- She states she wants to get off of the oxycodone “for the baby”
- Pain is improved, unsure if she is always taking oxycodone for reasons of pain
Case Vignette
Pregnant Woman on Oxycodone

- Oxycodone is helpful for the energy she needs to get through the day
- When she cuts back, she gets unmotivated, irritable, and fatigued. Her back pain also worsens, especially at night and before getting up in the morning.
- Oxycodone prevents the runny nose and eyes, yawning, that is problematic at her workplace.
- No routine alcohol, special occasions only, none since pregnant
- Quit smoking in college on advice of her Ob/gyn
Case Vignette
Clinical Questions

1. What criteria does this patient have for opioid use disorder?

2. Does this patient demonstrate a high risk for aberrant medication taking behaviors?

3. How does the clinical history contribute to any consideration of an opioid taper?
The “Gold Standard” of care for pregnant women with opioid use disorder is methadone maintenance.

Buprenorphine is an approved medication for the outpatient treatment of opioid use disorder since 2002 and is being used with increasing frequency for maintenance treatment of pregnant women with opioid use disorder.

Evidence suggests buprenorphine may cause a less severe withdrawal syndrome in the neonate compared to methadone.
How Did We Get Here?

History of Opioid Agonist Treatment and Pregnancy
How did Methadone Become the Standard?

**Why Methadone?**

- Can be taken orally
- Long acting property allows for once daily doses, necessary for observed dosing
- Established in the 1960’s as improving outcomes for pregnant women using IV heroin
Methadone Tapers

1960’s Theory – It would make sense for pregnant women to get off drugs completely, even prescribed ones.

- Initially in 1960’s methadone tapers were used and associated with:
  - high relapse rates
  - less prenatal care
  - worse outcomes for moms and babies
Why Maintenance and Not Tapers/ “Detox”?  

- Taper Changed To Maintenance dosing

  - This was associated with increased prenatal care and improved maternal and fetal outcomes compared to illicit heroin use
We Have Methadone! Problem Solved?

1960-1970’s Data:
• Daily methadone dosing improved maternal and fetal outcomes *(compared to illicit IV heroin use)*

Problem solved? No!

Maintenance on *long-acting* methadone led to *more prolonged and severe neonatal abstinence syndrome* (NAS) as compared to short-acting *heroin*
More Severe NAS with Methadone

Attempts to reduce NAS

• 1970’s: Again tapers and low doses were used but → worse neonatal outcomes

Despite worse outcomes:

• Late 1970’s Regulations: pregnant women must be maintained on low doses (<20 mg)
What Changed?
HIV Epidemic ➔ New Priorities

HIV Epidemic Changed Dosing Practices in the 1980-90’s:

Maternal-to-fetal HIV among IVDU

- Elimination of IV drug injection & neonatal HIV infection became higher priorities than reduction of NAS

Source: UNAIDS 2012
Methadone maintenance is recommended as the standard of care for opioid use disorder during pregnancy.
Still Searching for Options in Addiction Treatment

- Methadone
  - Unofficial standard of care x 40 years
  - NIH standard of care since 1997
- Desire to reduce MMT-induced NAS
- Buprenorphine approved for office based treatment 2002
- Milder withdrawal syndrome noted in adults with buprenorphine
- Studies evaluated buprenorphine and NAS
Buprenorphine: Partial Agonist Properties

- Buprenorphine: Partial Agonist Properties
MOTHER Study
Multisite Randomized Controlled Trial

- Compared maternal and neonatal outcomes in opioid-addicted women treated with methadone vs. buprenorphine (86 bup / 89 methadone)

- Outcomes for Buprenorphine treated arm:
  - Less infant morphine needed for NAS
  - Shorter infant hospital stays
  - Higher maternal dropout rate compared to methadone, mostly due to drug dissatisfaction

MOTHER Study
Drop-out Rates

• Higher drop-out rate (33%) in buprenorphine treated arm
  - higher patient dissatisfaction with buprenorphine cited as reason
  - 28 total patients dropout, 20 due to dissatisfaction with medication

• Lower Drop-out rate (18%) with methadone, less dissatisfaction
  - Only 2 due to dissatisfaction with medication
Pharmocology of Buprenorphine and Other non-NAS Benefits

Compared to methadone, buprenorphine has:

- Less suppression of fetal breathing, movement, and heart rate (NST)
- Fewer drug interactions
- Less QTc prolongation
- Fewer dosing changes required in pregnancy
- Fewer regulatory and logistical obstacles to split dosing
Anecdotal Observation of Pregnant Patient Trends

- Many pregnant women self-refer to opioid treatment programs for methadone or to office based physicians for buprenorphine.
- Many women enter treatment requesting “detox” or medically managed withdrawal (taper), often under pressure from family.

The point is that many women have not been assessed or counseled regarding the best option for treatment.
Maintenance VS. Medically Managed Withdrawal

- The 1997 NIH standard of care, which was maintenance treatment with methadone, was based on experience primarily of the 60’s and 70’s.
- This experience was based on information gathered from an IV heroin using pregnant population.
- The modern epidemic has a large proportion of pregnant women with primarily misuse and addiction to prescription opioids.
More Comparisons Between the 60’s-70’s and Modern Obstetrics

• The 60’s and 70’s was also an era with few non-invasive options for monitoring fetal well-being

• Modern fetal surveillance techniques are non-invasive, readily available
The Question:

Is it Time to Revisit Tapering or Detoxification for Some Pregnant Women with Opioid Use Disorder?

OR

Is there a select group of pregnant women with opioid use disorder who can safely undergo medically managed withdrawal and maintain abstinence?

Would this group be non-IV, non-heroin users?
“Active or passive maternal detoxification is associated with increased risk of fetal distress and fetal loss.” (Hudak ML, Tan RC, The Committee on Drugs and the Committee on Fetus and Newborn. (2012). Neonatal Drug Withdrawal. *Pediatrics*, 129(2):e540-60.)

This statement likely also draws on the experience of 60’s-70’s

Based on this traditional teaching, most pregnant women are denied the ability to medically withdraw from opioids. BUT………

• We should critically examine the evidence for this teaching.
Evidence For Fetal Distress related to Opioid Withdrawal

Much of this teaching is based on a case report by Zuspan in a 1975 article.

In the introduction to the 1975 article, Zuspan discusses a 1973 FDA edict, which required that methadone-treated women must be withdrawn within 21 days once the pregnancy is verified.

By 1975, this edict had been rescinded.
• Zuspan states that an intrauterine fetal demise, which had occurred during the 1973 time period when the edict was in effect, was attributed to withdrawal due to an association of “violent intrauterine movements” prior to the stillbirth.

• Based on that prior stillbirth, Zuspan’s program began a more gradual detoxification with monitoring of amniotic fluid amines to mark the neuroendocrine status of the fetus.
The article then describes a case report of fetal stress:

- Serial amniotic fluid epinephrine and norepinephrine levels showed a marked stress fetal response (during dose reduction) that was blunted when the methadone dose was increased.
- Based on this single case, the conclusion was that “Detoxification during pregnancy is not recommended unless the fetus can be biochemically monitored.”
Thus, we have a mention of a prior intrauterine fetal demise attributed to a 21 day methadone taper in a 1975 article introduction (but unpublished as a case report) accompanying a case report of fetal neuroendocrine stress based on amniotic fluid epinephrine and norepinephrine measurement performed during a more gradual methadone taper.

Let us continue to review the evidence.
Evidence for Fetal Loss

The historical warning against fetal loss related to opioid withdrawal also stems from a case report:

Narcotic withdrawal in pregnancy: Stillbirth incidence with a case report.
Rementeria 1973

The fetal loss in this 1973 case report referred to a woman at 39 weeks using illicit heroin and illicit methadone who developed withdrawal symptoms, went into labor and delivered a stillborn infant with meconium aspiration.
In the commentary, there is a good review of reports of intrauterine and neonatal deaths among opioid dependent women reported up until that time, but none specifically related to medically supervised tapers.
Modern Day Applications

- These oft-quoted articles by Zuspan and Rementeria, based on available 1970’s standards of care, inform us that women with chronic illicit opioid use and/or intermittent methadone treatment at low or tapering doses carry a risk of fetal death and distress in situations of rapid and/or essentially unmonitored methadone tapers.

- Whether this information should now inform us forty years later, when non-invasive fetal surveillance techniques are available, to prohibit gradual medically supervised tapers is left to question.
An Alternative Teaching

“Women can be safely withdrawn from opioids during Pregnancy” i.e., risks of fetal stress, loss are overstated

The question is whether it should be done

- A high rate of relapse in women with opioid use disorder places fetus at risk

NCSACW Webinar Series August 2011, Kaltenbach, Otero
“MSW” (Medically Supervised Withdrawal)="Detox") Data

A retrospective study of MSW, 1990-1996, Parkland Hospital

- Singleton gestations, inpatient detoxification, multi-disciplinary case-management program
- Medications used: clonidine or methadone
- Taper began at 24 weeks
- Maximum methadone dose range 10-85 mg
- Median time of taper 12 days (range 3-39 days)
- Unspecified:
  - How many patients were offered MSW or were excluded
  - If post MSW treatment offered or accepted by the patients
- Exclusion criteria: Pregnancies with poor growth or low amniotic fluid

34 women elected MSW

20 (59%) were successful and did not relapse before delivery

10 (29%) resumed street opioid use

4 (12%) did not complete MSW, chose MMT.

- No evidence of fetal distress during MSW, no fetal death, and no delivery before 36 weeks.

Conclusion: In selected patients, opioid MSW was safe during pregnancy
“MSW” (Medically Supervised Withdrawal)+ (“Detox”) Data

• 2003 retrospective case study: 101 women offered 21 day methadone taper.
• Unspecified: how many were excluded or declined
• 42 completed procedure.

• Obstetrical events during inpatient withdrawal management (reported by treatment episodes, not individual women)
  • 5 first trimester treatment episodes with 1 miscarriage
  • 54 2nd trimester treatment episodes; no obstetrical problems
  • 57 3rd trimester treatment episodes; 1 premature delivery

Conclusion: Methadone detoxification was not associated with any increased risk of miscarriage in the second trimester or premature delivery in the third trimester

Review of follow-up birth records for 24 of 50 women from original cohort:
• 10 completed withdrawal management during peripartum period
• average birth weight 5 lbs 10 oz
• only 1 woman was abstinent at the time of delivery

“MSW” (Medically supervised withdrawal)="detox" data

The Dashe and Luty studies suggest that the primary risk of MSW is **relapse** as opposed to fetal distress, fetal death, premature delivery, or 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester pregnancy loss from opioid withdrawal.

**New Question:**
Can **relapse** be avoided in pregnant women misusing or addicted only to prescription opioids?
Relapse Prevention in Pregnant Women With Opioid Use Disorder to Prescription Opioids

Retrospective cohort of pregnant opioid users 2006-2011 undergoing MSW with methadone in an inpatient hospital setting

- Offered MSW to all opioid users, including MMT patients and polysubstance users in unspecified numbers
- Exclusion criteria: fetal growth restriction, oligohydramnios, significant maternal psychiatric illness, or prior unsuccessful MSW attempt

95 women delivered with maternal and neonatal outcomes available for analysis

- 53 (56%) successfully completed, no relapse by delivery
- 17 (18%) did not complete MSW, chose agonist Rx
- 19 (20%) left the program
- 3 (3%) had fetal demise, not during hospitalization

Not So Select Populations

Median hospital stay for opioid withdrawal management differed significantly by group (p<0.001):

- Women who were opioid free at delivery stayed for median of 25 days
- Women who relapsed by delivery stayed for median of 15 days

**NO ASSOCIATION OF OUTCOMES WITH:**
- ROUTE OF ILLICIT OPIOID ADMINISTRATION
- AMOUNT OF DAILY ILLICIT OPIOID USE
- YEARS OF ILLICIT OPIOID USE
Where Are We Now?

• The three studies suggest inpatient MSW is possible without significant risk to fetus with considerations:
  ▪ Exclusion of fetus’ already at risk, i.e. growth retardation, oligohydramnios
  ▪ Close fetal monitoring at > 24 weeks
  ▪ Success in these studies is associated with intensive treatment and prolonged hospitalization
Where Are We Now?

• The big surprise is no finding of association between MSW resulting in positive neonatal outcomes and maternal drug history.

• The theory that non-IV, non- heroin using pregnant women may have better success with MSW than IV heroin users has not been yet established, based on one study (Stewart).

• Lesser addictive severity is generally a good prognostic indicator so further study is warranted.
Can This Be Applied in Practice?

• The data opens the door to cautious study of medically supervised withdrawal for the treatment of opioid use disorder during pregnancy because of reassuring safety data in these studies.

• Fetal assessment prior to consideration of MSW is critical.

• Unanswered questions:
  ▪ Is hospitalization necessary?
  ▪ Can outpatient tapers be safe and successful?
  ▪ Should demographics and drug history influence treatment options?
References


References


References

References

- Substance Abuse and Mental Health Services Administration. (2011). Results from the 2010 national survey on drug use and health: summary of national findings, NSDUH series H-41, HHS publication no. (SMA) 11-4658. Substance Abuse and Mental Health Services Administration, Rockville, MD.
PCSS-MAT Mentoring Program

- PCSS-MAT Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.

- PCSS-MAT Mentors comprise a national network of trained providers with expertise in medication-assisted treatment, addictions and clinical education.

- Our 3-tiered mentoring approach allows every mentor/mentee relationship to be unique and catered to the specific needs of both parties.

- The mentoring program is available, at no cost to providers.

For more information on requesting or becoming a mentor visit: pcssmat.org/mentoring
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A simple and direct way to receive an answer related to medication-assisted treatment. Designed to provide a prompt response to simple practice-related questions.

Ask Now
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For More Information: www.pcssmat.org

Twitter: @PCSSProjects

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